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(21) International Application Number: PCT/US96/05241 (22) International Filing Date: 16 April 1996 (16.04.96) (30) Priority Data: 08/431,170 28 April 1995 (28.04.95) US (71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: ADORANTE, Joseph, S.; 1546 Thorn Tree Lane, Irvine, CA 92715 (US). WOLDEMUSSIE, Elizabeth; 40 Gullwing Avenue, Laguna Niguel, CA 92677 (US). RUIZ, Guadalupe; 1068 Gentle Drive, Corona, CA 91720 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, 2525 Dupont Drive, T-2, 2-E, P.O. Box 19534, Irvine, CA 92713-9534 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i>
(54) Title: METHOD FOR REDUCING INTRAOCULAR PRESSURE IN THE MAMMALIAN EYE BY ADMINISTRATION OF POTASSIUM CHANNEL BLOCKERS		
(57) Abstract Pharmaceutical compositions and a method are disclosed for treating glaucoma and/or ocular hypertension in the mammalian eye by administering to the mammalian eye the pharmaceutical composition of the invention which contains, as the active ingredient, one or more compounds having potassium channel blocking activity. Examples of potassium channel blockers utilized in the pharmaceutical composition and method of treatment are quinine, tremogenic indole alkaloids, such as Penitrem A and paspalicine, and insect toxins such as charybdotoxin and iberiotoxin.		

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METHOD FOR REDUCING INTRAOCULAR PRESSURE
IN THE MAMMALIAN EYE BY ADMINISTRATION
OF POTASSIUM CHANNEL BLOCKERS

5

BACKGROUND OF INVENTION

Field of the Invention

The present invention is directed to pharmaceutical
10 compositions, and primarily to topically applied ophthalmic
compositions comprising as the active ingredient one or more
compounds having the ability to block potassium channels in the ciliary
epithelium, e.g. to inhibit the transport of potassium ions and fluid
secretion in epithelia. The pharmaceutical compositions are useful for
15 reducing intraocular pressure in animals of the mammalian species. In
another aspect, the present invention is directed to administering such
formulations and compositions to animals of the mammalian species
(including humans) for reducing intraocular pressure in the eye.

20 Brief Description of the Art

Glaucoma is an optical neuropathy associated with elevated
intraocular pressures which are too high for normal function of the eye,
and results in irreversible loss of visual function. It is estimated in
25 medical science that glaucoma afflicts approximately 2 per cent of the
population over the age of forty years, and is therefore a serious health
problem. Ocular hypertension, i.e. the condition of elevated intraocular
pressure, which has not yet caused irreversible damage, is believed to
represent the earliest phase of glaucoma. Many therapeutic agents have
30 been devised and discovered in the prior art for the treatment or
amelioration of glaucoma and of the condition of increased intraocular
pressure which precedes glaucoma.

Primary open angle glaucoma (POAG) is associated with a rise in
intraocular pressure (IOP). This increase in IOP is believed to contribute
35 to the loss of optic nerve function which ultimately leads to blindness.

Reduction of IOP is therefore a crucial component in the management of POAG.

In principle, IOP can be reduced by inhibiting aqueous humor inflow or conversely by stimulating aqueous outflow. Aqueous humor inflow is mediated by ion transport across the ciliary epithelium. The above secretion of aqueous humor produced by the ciliary epithelium is then drained from the eye (aqueous outflow) via the trabecular meshwork into Schlemm's canal.

Because ion transport mediates secretion of aqueous humor, blocking or modulating the relevant ion channels or carriers will consequently inhibit or reduce aqueous formation and thus lower IOP. On the other hand, since the trabecular meshwork (TM) is a major obstacle (resistance pathway) to aqueous outflow, reducing its resistance to the passage of fluid should enhance outflow and lower IOP. Thus, by reducing the volume or size of TM cells it should be possible to enhance outflow by lowering the resistance to the passage of ocular fluid. Cell volume/size is determined by a balance between ion uptake and efflux mechanisms. Therefore, it follows that reducing TM cell volume can be accomplished by either stimulating the ion efflux or inhibiting the ion uptake mechanisms in this cell type.

The drugs currently utilized in the treatment of glaucoma include miotics (e.g., pilocarpine, carbachol, and acetylcholinesterase inhibitors), sympathomimetics (e.g., epinephrine and dipivalylepinephrine), beta-blockers (e.g., betaxolol, levobunolol and timolol), alpha-2 agonists (e.g., para-amino clonidine) and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide). Miotics and sympathomimetics are believed to lower intraocular pressure by increasing the outflow of aqueous humor, while beta-blockers, alpha-2 agonists and carbonic anhydrase inhibitors are believed to lower intraocular pressure by decreasing the formation of aqueous humor. All five types of drugs have potential side effects. Miotics, such as pilocarpine, can cause blurring of vision and other visual side effects which may either decrease patient compliance or require termination of miotic drug therapy. Carbonic anhydrase inhibitors can also cause serious side effects which affect patient compliance and/or necessitate

withdrawal of the drug therapy. At least one beta-blocker, timolol, has increasingly become associated with serious pulmonary side effects attributable to its effect on beta-2 receptors in pulmonary tissue.

As a result additional antiglaucoma drugs are being developed,
5 e.g., prostaglandin derivatives, muscarinic antagonists, etc.

In light of the foregoing circumstances, it is clear that a need exists for new, more potent antiglaucoma compositions which avoid or reduce the above-cited side effects and enhance patient compliance, since the foregoing and other anti-glaucoma and ocular hypotensive compounds
10 and agents of the prior art do not provide a treatment or cure for glaucoma and ocular hypertension which is satisfactory in all respects. Therefore, the pharmacological and related arts and sciences continue searching for additional and better anti-glaucoma and ocular hypotensive agents.

15 Chloride channel blockers such as 5-nitro-2-(3-phenylpropylamino)-benzoate (NPPB) have been shown to inhibit Cl⁻ transport and fluid secretion/absorption in rat intestine. (See for example, Acta Physiol Scand: No. 149, 1993: pp. 365-376, Fryklund et al., "The effects of potassium transport inhibitors on intestinal fluid and ion
20 transport in vivo and in vitro".)

The use of chloride-channel blockers for reducing the intraocular pressure in the eye of a mammal is disclosed and claimed in U.S. Patent Application Serial No. 346,660, which was filed on November 30, 1994 in the names of Adorante et al, which is herein incorporated by reference
25 in its entirety.

In addition, PCT Patent WO 89/10757 discloses the use of potassium channel openers for treating glaucoma.

SUMMARY OF THE INVENTION

30 Surprisingly it has been discovered in accordance with the present invention that potassium channel blockers are effective as anti-glaucoma agents and as agents for reducing intraocular pressure, when such agents are applied to the mammalian eye in a pharmaceutical composition, preferably in a topical ophthalmic composition.

35 Accordingly, the present invention relates to a method of treating

glaucoma, or ocular hypertension by topically administering to the mammalian eye an ophthalmic composition which contains an effective amount of a potassium channel blocker. In particular, to inhibit aqueous humor production (inflow inhibition), the potassium channel that resides at the basolateral membrane of the nonpigmented ciliary epithelial cell (NPE) may be blocked. It is believed that blocking the potassium channel of the NPE cell will inhibit net solute and H₂O efflux and therefore aqueous secretion that will in turn will lower IOP. Some preferred examples of potassium channel blockers are quinine, tremogenic indole alkaloids such as Penitrem A and paspalicine, and insect toxins such as charybdotoxin and iberiotoxin. In particular tremogenic indole alkaloids should be especially potent in blocking the potassium channels of NPE cells since these compounds are highly specific in blocking Ca²⁺-gated Maxi potassium channels: the potassium channel of the NPE cell appears to be a Ca²⁺-gated Maxi potassium channel. Thus, aqueous secretion is inhibited and hence intraocular pressure (IOP) is lowered by blocking potassium channels in the NPE cells.

The ophthalmic compositions of the invention contain the active ingredient in a concentration range of approximately 0.0001 to 0.1 per cent weight by volume. The composition itself includes, in addition to the active ingredient, such excipients which are per se well known in the art for preparing ophthalmic compositions, particularly ophthalmic solutions. In accordance with the method of the invention the ophthalmic compositions, preferably ophthalmic solutions are applied topically to the mammalian eye approximately 1 or 2 times daily.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the presence of the drug quinine on the regulatory volume decrease (RVD; a readout for net ion and H₂O efflux), on bovine nonpigmented ciliary epithelial (NPE) cells. Inhibition of RVD by quinine is consistent with the notion that Ca²⁺-gated K channels are important in solute and water movement (secretion) in ciliary epithelium.

Figure 2 is a graph showing the effect of intracameral administration of the drug quinine on the intraocular pressure (IOP) in the rabbit eye.

5 DETAILED DESCRIPTION OF THE INVENTION

The compounds which are utilized in accordance with the method of the present invention, and in the pharmaceutical compositions of the present invention, are potassium channel blockers. In this regard the term potassium channel blocker is defined as those
10 compounds or agents which inhibit net potassium flux (current) through a potassium specific pathway (channel, integral membrane protein) within biological membranes. Specific and preferred examples of potassium channel blockers which are utilized in accordance with the present invention are provided.

15 Pharmaceutically acceptable salts of the potassium channel blockers can also be used in accordance with the present invention. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the
20 context in which it is administered.

Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, such as alkali ions, e.g. sodium, potassium, etc. Organic amine salts may be
25 made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines, e.g. alkyl amines wherein each alkyl group may comprise up to six carbon atoms, or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. It is only important that the cation of any salt of a potassium channel blocker
30 utilized in the compositions or methods of this invention be able to block potassium channels in the ciliary epithelium.

For reducing intraocular pressure in a mammalian eye, and particularly for treatment of glaucoma in humans suffering from that condition, the active compounds (or mixtures or salts thereof) are
35 administered in accordance with the present invention to the eye

admixed with an ophthalmically acceptable carrier. Any suitable, e.g., conventional, ophthalmically acceptable carrier may be employed. A carrier is ophthalmically acceptable if it has substantially no long term or permanent detrimental effect on the eye to which it is administered.

5 Examples of ophthalmically acceptable carriers include water (distilled or deionized water), saline and other aqueous media. In accordance with the invention, the active compounds are preferably soluble in the carrier which is employed for their administration, so that the active compounds are administered to the eye in the form of a solution.

10 Alternatively, a suspension of the active compound or compounds (or salts thereof) in a suitable carrier may also be employed.

In accordance with the invention the active compounds (or mixtures or salts thereof) are administered in an ophthalmically acceptable carrier in sufficient concentration so as to deliver an effective
15 amount of the active compound or compounds to the eye. Preferably, the ophthalmic, therapeutic solutions contain one or more of the active compounds in a concentration range of approximately 0.0001% to approximately 1% (weight by volume) and more preferably approximately 0.0005% to approximately 0.1% (weight by volume).

20 Any method of administering drugs directly to a mammalian eye may be employed to administer, in accordance with the present invention, the active compound or compounds to the eye to be treated. By the term "administering directly" is meant to exclude those general systemic drug administration modes, e.g., injection directly into the
25 patient's blood vessels, oral administration and the like, which result in the compound or compounds being systemically available. The primary effect on the mammal resulting from the direct administering of the active compound or compounds to the mammal's eye is preferably a reduction in intraocular pressure. More preferably, the active useful
30 compound or compounds are applied topically to the eye or are injected directly into the eye. Particularly useful results are obtained when the compound or compounds are applied topically to the eye in an ophthalmic solution, i.e. as ocular drops.

35 Topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose

delivery and fewer systemic side effects, such as cardiovascular hypotention. An exemplary topical ophthalmic formulation is shown below in Table I. The abbreviation q.s. means a quantity sufficient to effect the result or to make volume.

5

TABLE I

<u>Ingredient</u>	<u>Amount(% W/V)</u>
10 Active Compound in accordance with the invention,	about 0.0001 to about 1
Preservative	0-0.10
Vehicle	0-40
Tonicity Adjustor	1-10
15 Buffer	0.01-10
pH Adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
Purified Water	as needed to make 100%

20

Various preservatives may be used in the ophthalmic preparation described in Table I above. Preferred preservatives include, but are not limited to, benzalkonium potassium, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate. Likewise, various preferred vehicles may be used in such ophthalmic preparation. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose and hydroxyethyl cellulose.

25

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium potassium, potassium potassium etc., mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

30

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include but are not limited to, acetate buffers, citrate buffers,

35

phosphate buffers, and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene.

The ophthalmic solution (ocular drops) may be administered to the mammalian eye as often as necessary to maintain an acceptable level of intraocular pressure in the eye. In other words, the ophthalmic solution (or other formulation) which contains the potassium channel blocker as the active ingredient, is administered to the mammalian eye as often as necessary to maintain the beneficial hypotensive effect of the active ingredient in the eye. Those skilled in the art will recognize that the frequency of administration depends on the precise nature of the active ingredient and its concentration in the ophthalmic formulation. Within these guidelines it is contemplated that the ophthalmic formulation of the present invention will be administered to the mammalian eye approximately once or twice daily.

Specific examples of potassium channel blockers which are used as the active effective ingredients in the ophthalmic compositions of the present invention are described and cited above.

A potassium channel blocker, in accordance with the present invention, may be identified by the method disclosed in Single-Channel Recording, Sakmann et al, published by Plenum Press. (See Chapter 21, by Camardo et al entitled Single-Channel Analysis in Aplysia Neurons A Specific K^+ Channel Is Modulated by Serotonin and Cyclic AMP.)

Potassium Channel blockers may also be identified in accordance with the method disclosed below in the Example.

EXAMPLES

The present invention is demonstrated by *in vitro* and *in vivo* data. In Figure 1, 100 μ M of quinine were found to depress the regulatory volume decrease (RVD) that occurs following hyposmotic swelling of bovine non-pigmented ciliary epithelial (NPE) cells. In this example, NPE cells were suspended in an isosmotic (295 mOsm) solution containing 100 μ M quinine for 30 minutes prior to suspension in a hyposmotic (198 mOsm) solution. Control cells were subjected to

the same hyposmotic solution but without quinine in the medium. Changes in cell volume were measured using a Coulter Counter interfaced to a Coulter Channelyzer. It is noted that, following osmotic swelling, control cells regulate towards their original isosmotic volume while quinine-treated cells remain swollen. The above findings indicate that quinine, via blocking of the potassium channel, inhibits solute and osmotically obliged H₂O efflux. Because the potassium-dependent ion flux pathways, activated following osmotic cell swelling of NPE cells, are involved in aqueous secretion, quinine will inhibit aqueous humor formation and, thus, lower IOP.

In the *in vivo* studies normotensive rabbits were injected intracamerally with 1 m M quinine. Figure 2 shows that 1m M quinine lowered IOP by 7 mm of Hg and IOP remained depressed for 24 hours. Taken together, the above *in vitro* and *in vivo* experiments demonstrate that blocking the potassium channel in the ciliary epithelium will reduce IOP.

One advantage potassium channel inhibition has over other IOP lowering therapies is that the effector, i.e. the ion channel or carrier, is targeted rather than the receptor. Since effector blockage is direct, it should be the most potent and effective way of inhibiting aqueous secretion and hence lowering IOP. On the other hand, targeting a receptor to block an effector is indirect and relies on modulation of a series of cellular events (intracellular messengers/signals) prior to effector inhibition.

In view of the above, it is clear that the scope of the present invention should be interpreted solely on the basis of the following claims, as such claims are read in light of the disclosure.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition useful for reducing
intraocular pressure in the eye of a mammal, the composition
5 comprising as its active ingredient one or more compounds having
potassium channel blocking activity.
2. The pharmaceutical composition of Claim 1 wherein the
compound having potassium channel blocking activity is selected from
10 the group consisting of quinine, tremogenic indole alkaloids and insect
toxins.
3. The pharmaceutical composition of Claim 2 wherein said
compound is selected from the group consisting of quinine, Penitrem A,
15 paspalicine, charybdotoxin and iberiotoxin.
4. The pharmaceutical composition of Claim 2 wherein the
compound having potassium channel blocking activity is quinine.
- 20 5. The pharmaceutical composition of Claim 2 wherein the
compound having potassium channel blocking activity is
charybdotoxin.
6. The pharmaceutical composition of Claim 2 where the
25 composition is an ophthalmic solution, adapted for administration to
the eye of a mammal in the form of eye droplets.
7. The pharmaceutical composition of Claim 2 wherein the
composition contains approximately 0.0001 to 1 per cent weight by
30 volume of said compound having potassium channel blocking activity.
8. A pharmaceutical composition useful for providing
neuroprotective activity in the eye of a mammal comprising as its active
35 ingredient one or more compounds having potassium channel blocking
activity.

9. The pharmaceutical composition of Claim 8 wherein the compound having potassium channel blocking activity is selected from the group consisting of tremogenic indole alkaloids and insect toxins.

5

10. The pharmaceutical composition of Claim 9 wherein said compound is selected from the group consisting of quinine, Penitrem A, paspalicine, charybdotoxin and iberiotoxin.

10 11. The pharmaceutical composition of Claim 9 wherein the compound having potassium channel blocking activity is quinine.

12. The pharmaceutical composition of Claim 9 wherein the compound having potassium channel blocking activity is
15 charybdotoxin.

13. The pharmaceutical composition of Claim 9 wherein the composition contains approximately 0.0001 to 1 percent weight by volume of said compound having potassium channel blocking activity.
20

14. A method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal comprising the step of administering to the mammal a pharmaceutical composition which comprises as its active
25 ingredient one or more compounds having potassium channel blocking activity.

15. The method of Claim 14 wherein the compound having potassium channel blocking activity is selected from the group
30 consisting of quinine, tremogenic indole alkaloids and insect toxins.

16. The method of Claim 15 wherein said compound is selected from the group consisting of quinine, Penitrem A, paspalicine, charybdotoxin and iberiotoxin.
35

17. The method of Claim 15 wherein the compound having potassium channel blocking activity is quinine.
18. The method of claim 15 wherein said compound having potassium channel blocking activity is charybdotoxin.
19. The method of treatment of Claim 15 wherein the composition is an ophthalmic solution adapted for administration to the eye of a mammal in the form of eye droplets.
20. The method of treatment of Claim 15 wherein in the ophthalmic composition the concentration of the compound having potassium channel blocking activity is in the range of approximately 0.0001 to 1 per cent weight by volume.
21. A method for providing neuroprotective effect to the eye of a mammal which comprises the step of administering to the mammal a pharmaceutical composition which comprises as its active ingredient one or more compounds having potassium channel blocking activity.
22. The method of Claim 20 wherein the compound having potassium channel blocking activity is selected from the group consisting of quinine, tremogenic indole alkaloids and insect toxins.
23. The method of Claim 22 wherein said compound is selected from the group consisting of quinine, Penitrem A, paspalicine, charybdotoxin and iberiotoxin.
24. The method of Claim 22 wherein the compound having potassium channel blocking activity is quinine.
25. The method of claim 22 wherein said compound having potassium channel blocking activity is charybdotoxin.

26. The method of Claim 22 wherein the composition contains approximately 0.0001 to 1 per cent weight by volume of said compound having potassium channel blocking activity.

5

AMENDED CLAIMS

[received by the International Bureau on 2 September 1996 (02.09.96);
original claims 2-4, 8-13, 15-17, 21-26 cancelled; original claims
5-7, 18-20 amended; new claims 1, 14, 27, 28 added;
remaining claims unchanged (3 pages)]

1. A pharmaceutical composition useful for reducing intraocular pressure in the eye of a mammal in need thereof, by blocking
- 5 Ca^{2+} - gated Maxi potassium channels, the composition comprising as its active ingredient a therapeutically effective amount of one or more compounds selected from the group consisting essentially of Penitrem A, paspalicine, charybdotoxin and iberiotoxin.
- 10 2. Deleted
3. Deleted
4. Deleted
- 15 5. The pharmaceutical composition of Claim 1 wherein the compound having potassium channel blocking activity is charybdotoxin.
- 20 6. The pharmaceutical composition of Claim 1 where the composition is an ophthalmic solution, adapted for administration to the eye of a mammal in the form of eye droplets.
- 25 7. The pharmaceutical composition of Claim 1 wherein the composition contains approximately 0.0001 to 1 per cent weight by volume of said compound having potassium channel blocking activity.
8. Deleted
- 30 9. Deleted
10. Deleted
- 35 11. Deleted

12. Deleted

13. Deleted

5 14. A method of treating animals of the mammalian species,
including humans, for the purpose of reducing intraocular pressure in
the eye of the mammal in need thereof comprising the step of
administering to the mammal a pharmaceutical composition which
10 comprises as its active ingredient a therapeutically effective amount of
one or more compounds selected from the group consisting essentially
of Penitrem A, paspalicine, charybdotoxin and iberiotoxin by blocking
Ca²⁺ - gated Maxi potassium channels.

15 15. Deleted

16. Deleted

17. Deleted

20 18. The method of claim 14 wherein said compound having
potassium channel blocking activity is charybdotoxin.

25 19. The method of treatment of Claim 14 wherein the
composition is an ophthalmic solution adapted for administration to
the eye of a mammal in the form of eye droplets.

30 20. The method of treatment of Claim 14 wherein in the
ophthalmic composition the concentration of the compound having
potassium channel blocking activity is in the range of approximately
0.0001 to 1 per cent weight by volume.

21. Deleted

35 22. Deleted

23. Deleted
24. Deleted
- 5 25. Deleted
26. Deleted
- 10 27. The pharmaceutical composition of claim 1 wherein said compound is selected from the group consisting essentially of Penitrem A and paspalicine.
- 15 28. The method of claim 14 wherein said compound is selected from the group consisting essentially of Penitrem A and paspalicine.

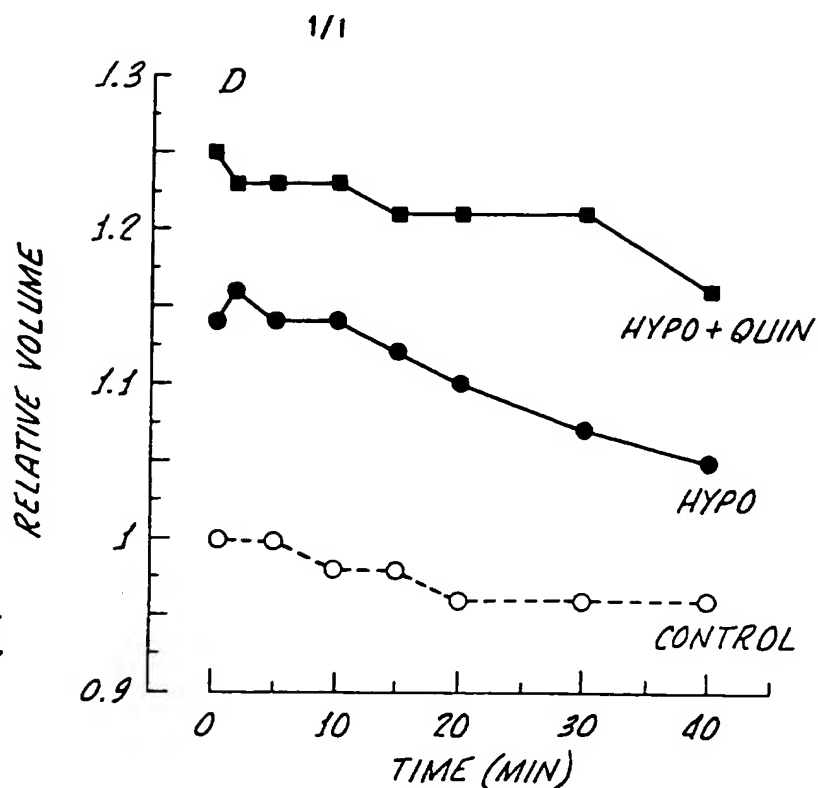


FIG. 1.

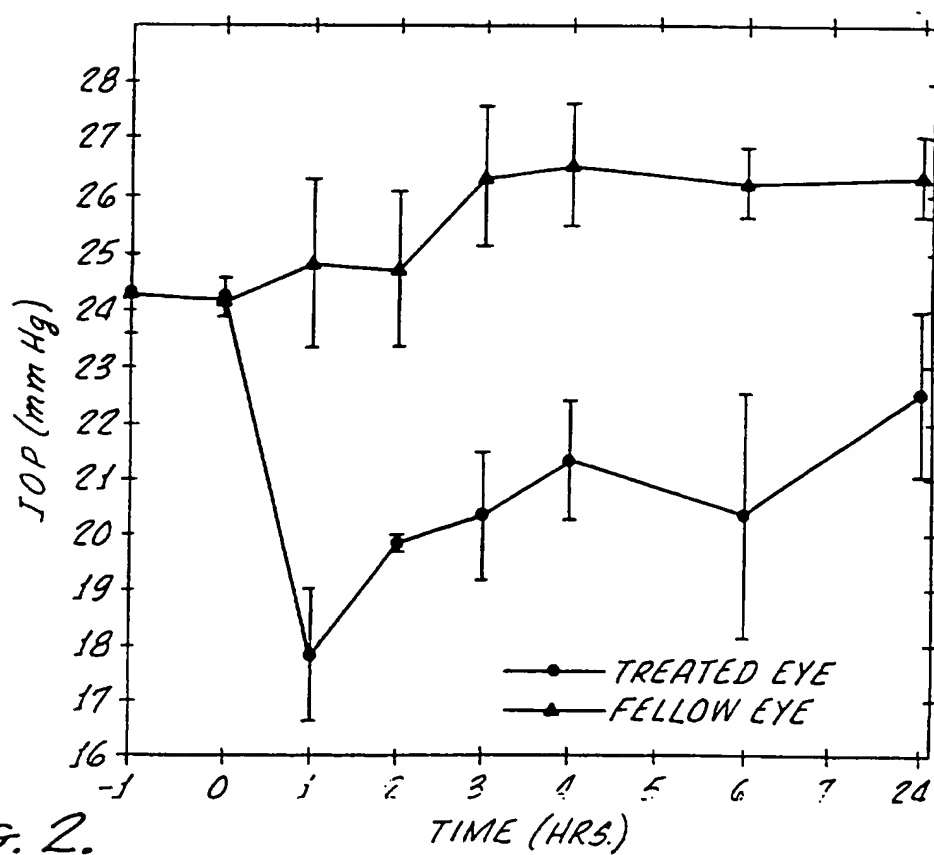


FIG. 2.

INTERNATIONAL SEARCH REPORT

Inter ١٢١ Application No
PCT/US 96/05241

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 28900 (VIDE PHARMACEUTICALS) 22 December 1994 see the whole document ---	1-26
X	WO,A,94 18967 (HARVARD COLLEGE) 1 September 1994 see page 1, line 16 ---	1-26
A	WO,A,89 10757 (LEO PHARM PROD LTD) 16 November 1989 cited in the application see the whole document -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

9 July 1996

Date of mailing of the international search report

18.07.96

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/05241

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-26 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter Application No
PCT/US 96/05241

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9428900	22-12-94	AU-B- 7099194	03-01-95
WO-A-9418967	01-09-94	US-A- 5512591	30-04-96
		AU-B- 6243494	14-09-94
		EP-A- 0644760	29-03-95
WO-A-8910757	16-11-89	AU-B- 3693789	29-11-89